REMARKS

Claims 1-5, 7-8, 10-14 and 18-20 are pending and under examination. Claims 6, 9 and 15-17 have been withdrawn from consideration. Applicants reserve the right to pursue these claims in a later filed application claiming the benefit of priority to the above-identified application. Applicants have reviewed the Office Action mailed February 16, 2007, and respectfully traverse all issues for the reasons that follow.

Priority

Applicants acknowledge and thank the Examiner for clarifying that claims 1-14 and 18-20 are entitled to the benefit of priority to provisional application serial numbers 60/417,511 and 60/444,933. The Examiner maintains that provisional application serial number 60/395,763, filed July 10, 2002, (the '763 application) fails to provide adequate support or enablement for claims 1-5, 7-8, 10-14 and 18-20.

Applicants maintain that the prior application provides sufficient support and enablement to satisfy the requirements of § 112, first paragraph. For example, the '763 application describes that a "computational framework is developed for the identification of optimal gene knockout candidates ensuring that the optimal growth patterns of the resulting metabolic networks overproduce desired biochemicals" (see, for example, Summary of the Invention at page 1). With respect to the computational framework, the application also describes and teaches:

> An MILP-based formulation for suggesting optimal gene knockouts was developed drawing upon the same duality theory concepts applied to the metabolic objective function determination formulation.

Application at page 2, lines 7-9.

The above passages describe and teach a computational framework that couples both a cellular objective with a bioengineering objective because the method applies metabolic

objective function determination for optimization of both a desired biochemical and growth. The subject application exemplifies this support in the `763 application when it describes the use of duality theory for coupling a cellular objective with a metabolic objective (see, for example, paragraph 0020). Accordingly, the `763 application provides sufficient support to satisfy the written description and enablement requirements and withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph, for lacking enablement allegedly because the claim is directed to any optimization problem, but that the specification enables only linear optimization. Referring to the reasons provided in the rejection of record, the Examiner alleges that the term "optimization problem" is interpreted to mean "any method that results in attaining a biological objective and a cellular objective" (Office Action, p. 4, para. 1 (emphasis added)), including those not yet conceived, and that the specification lacks formation of optimization problems other than bilevel optimization. Relying on Papin et al., *Trends in Biochem. Sci.* 28:250-58 (2003), the Examiner further alleges that an algorithm does not exist which can "solve the problem in polynomial time," alleging an "undue burden" [*sic*] for determining which networks can be subject to reduction in order to produce a computationally tractable problem.

The enablement requirement of the first paragraph of § 112 requires the specification to teach those skilled in the art how to make and use the claimed invention without undue experimentation. *Genentech, Inc. v. Novo Nodisk A/S*, 108 F.3d 1361, 1365, 42 U.S.P.Q.2d 1001, 1004 (Fed. Cir. 1997), *see also* MPEP §2164.01(c), fourth paragraph. Applicants submit that the subject application satisfies this requirement.

Applicants claim a method for determining candidates for gene deletions and additions using a model of a metabolic network which employs a mathematical optimization problem that couples at least one cellular objective with a bioengineering objective. Optimization problems are well known in the art and involve using mathematical optimization methods to solve for an optimal solution to an objective or stated function. The claimed invention couples the solution for the two objective functions corresponding to at least one cellular objective and a bioengineering objective.

Solving for an objective function is distinct from the alleged interpretation of a "method that results in attaining a biological objective and a cellular objective." *Id.* For example, optimization methods do not attain an objective. Rather, an objective is stated and the methods solve for its solution. The term "objective function" and optimization methods are well known to those skilled in the art. In this regard, Applicants respectfully point out that the National Institute of Standards and Technology defines an optimization problem to be:

> A computational problem in which the object is to find the best of all possible solutions. More formally, find a solution in the feasible region which has the minimum (or maximum) value of the objective function.
> *National Institute of Standards and Technology.* NIST 2005. http://www.nist.gov/ (11 Feb. 2005) (*citing Algorithms and Theory of Computation Handbook*, pages 29-20 and 34-17, Copyright 1999 by CRC Press LLC. *Appearing in the Dictionary of Computer Science, Engineering and Technology*, Copyright 2000 CRC Press LLC.

This definition includes problems that find a solution within a feasible region additional to linear optimization problems and also defines the optimization problem as a solution which has a minimum or maximum value of the objective function. The meaning of an objective function is similarly well known in the art and is defined by the National Institute of Standards and Technology to mean:

> A function associated with an optimization problem which determines how good a solution is.

Id.

In light of the above, Applicants maintain that the teachings and guidance in the application are sufficient to enable optimization methods other than linear optimization. Applicants' previous response point out two such optimization methods exemplified in the application. Given such teachings and guidance in the application that the claimed method couples two objective functions in its solution, those skilled in the art will understand that other well known optimization procedures also can be used to perform the methods of the claimed invention. Moreover, the assertion that Applicants are claiming use of optimization problems not yet conceived and that it would be an undue burden to those skilled in the art is unfounded. The claims are directed to forming an optimization problem and solving it for coupled objectives. Hence, Applicants are not claiming all optimization problems. Rather, only those optimization methods that can be formulated to couple two objective functions, namely a cellular objective and a bioengineering objective, and solved for its solution are within the scope of the claims. Those skilled in the art will understand which optimization methods allow coupling of two objective functions without undue experimentation.

The citation of Papin et al. also appears to be misinterpreted as applicable to the teachings and guidance in the application with respect to the claimed invention. The cited passage in Papain et al. relied upon by the Examiner is not pertinent to mathematical optimization problems. Rather, this passage is directed to convex basis computational methods which are described by Papin et al. to be NP-complete problems. This method is used to mathematically describe, for example, the structural properties of a network. Convex basis methods or NP-complete problems are distinct from optimization methods because there is no formulation of an objective or stated

function. In contrast, an optimization method solves for an optimal solution to an objective function of a network. In the claimed methods, there are at least a pair of coupled objective functions, which are a cellular objective and a bioengineering objective. The claimed optimization methods solve for maximizing or minimizing these stated objectives under a given set of conditions. Therefore, reliance on the passage in Papin et al. as support for this ground of rejection is unfounded because convex basis methods are distinct and dissimilar to the claimed methods of forming and solving an optimization problem that couples at least one cellular objective with a bioengineering objective.

In light of the teachings and guidance in the application as well as the well known methods of optimization which solve for an objective function, Applicants maintain that the application sufficiently satisfy the requirements of § 112, first paragraph. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1-5, 7-8, 10-14 and 18-20 stand rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Burgard et al., *Biotechnology and Bioengineering* 74:364-375 (2001), in view of Yang et al., *Metabolic Engineering* 1:26-34 (1999) and further in view of Voit, *Biotechnology and Bioengineering* 40:572-82 (1992). Quoting a portion of the abstract, the Examiner alleges that Burgard et al. "clearly teach" the element of forming an optimization problem that couples at least one cellular objective with at least one bioenginnering objective. To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (C.C.P.A. 1974); M.P.E.P. §2143.03.

Applicants respectfully submit that the Examiner's cited support and rationale appear to be unfounded. Accordingly, the Examiner has not established a *prima facie* case of obviousness at least because the cited combination of references fail to teach or suggest coupling at least one cellular objective with at least one bioengineering objective.

All independent claims recite the element of coupling at least one cellular objective with at least one bioengineering objective. Applicants' previous response particularly pointed out this deficiency in the cited combination of art (see, for example, Response filed December 19, 2006, at page 10, paragraph 3). Applicants' previous response also pointed out that amino acid formation is an example of a bioengineering objective whereas biomass production is an example of a cellular objective. As set forth above, an optimization problem provides a solution for the objective function to an optimization problem. In contrast to the Examiner's assertion, the mere fact that a cellular characteristic is a measure of a model's performance does not mean that it is part of the optimization problem. Therefore, unless a cellular characteristic is an objective function to an optimization problem it is not part of the solution to the problem and cannot be coupled to a second, different objective function such as a bioengineering objective as a solution to the claimed optimization problem.

The passage in Burgard et al. quoted by the Examiner fails to teach or suggest the coupling of one objective function corresponding to a cellular objective and a second objective function corresponding to a bioengineering objective. Rather, the passage in general, and Burgard et al. in particular, describe network performance in models having both gene additions and deletions. Biomass was used as a measure of performance and aerobic growth, emphasized by the Examiner, merely characterizes the growth conditions of the studies. Therefore, where the quoted passage states that "[t]he developed modeling and optimization framework is tested by

investigating the effect of gene deletions on biomass production and the maximum theoretical production of the 20 amino acids for aerobic growth on glucose and acetate substrates," the reference to biomass is merely a measure of performance, not a cellular objective. Similarly, the reference to aerobic growth merely describes that the model was run under growth conditions simulating little or no oxygen.

There is no teaching or suggestion in the cited passage or in Burgard et al. that aerobic growth is an objective function to an optimization problem much less any teaching or suggestion that aerobic growth is an objective function that is coupled to a second objective function corresponding to a bioengineering objective. Absence a teaching or suggestion in the cited references of each of the elements of the claimed method to coupling a cellular objective with a bioengineering objective, the Office has not established a *prima facie* case of obviousness of any of the claims under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

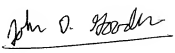
CONCLUSION

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

Please consider this a Request for three month extension of time under 37 C.F.R. 1.136 from May 16, 2007 to August 16, 2007 and charge Deposit Account No. 26-0084 the amount of $510.00 for this extension. No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



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